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European Surveillance of Antimicrobial Consumption (ESAC): Data Collection Performance and Methodological Approach

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Background
Europe is a continent with strong public healthcare systems, but diverging antibiotic policies and resistance patterns.

Aims
To describe the performance and methodological approach in a retrospective data collection effort (1997–2001), through an international network of surveillance systems, aiming to collect publicly available, comparable and reliable data on antibiotic use in Europe.

Methods
A central multidisciplinary management team co-ordinated a network of national representatives, liasing with national data providers and bodies responsible for antibiotic policy. The data collected were screened for bias, using a checklist. We focused on detection bias in sample and census data; errors in assigning medicinal product packages to the Anatomical Therapeutic Chemical Classification (ATC); errors in calculations of defined daily doses (DDD) per package; bias by over-the-counter sales and parallel trade; and bias in ambulatory care (AC)/hospital care (HC) mix. Datasets were corrected after national feedback, and classified as valid; valid but with minor bias; not valid.

Results
Of the 31 participating countries, 21 countries delivered AC data suitable for cross-national comparison (14 for all 5 years). Of these, 17 countries provided data on a quarterly basis for at least 1 year. For HC, 14 countries were able to deliver valid data (nine for all 5 years). A valid estimate of the total exposure of national populations to human antibiotic consumption could be made in 17 countries.

Conclusion
In cross-national comparisons of antibiotic consumption in Europe, methodological rigour in correcting for various sources of bias and checking the validity of ATC/DDD assignment is needed.

Introduction

Antibiotic consumption is probably a major trigger for the development of antibiotic resistance. Several calls to stop the excessive use of antibiotics have been made [1, 2]. Nevertheless, both consumption and resistance are tending towards escalation. Particularly in the southern countries of Europe, resistance is reaching alarming levels. This worrying trend has also begun in Central Europe. With the increase in travel and trade across the European Union (EU) over recent years, the risk of dissemination of antibiotic-resistant pathogens grows. To prevent the further spread of resistance and to develop effective strategies to foster appropriate antibiotic use in all European countries, international cooperation is necessary [3], starting with setting up reliable surveillance systems of both antibiotic resistance and consumption.

With regard to antimicrobial resistance, the European Antimicrobial Resistance Surveillance System (EARSS) has been operational since 1999 [4].

In 2001 the European Commission (Directorate-General Sanco – Health Monitoring Program) established the European Surveillance of Antimicrobial Consumption (ESAC) project [5]. The aim of the project was to collect comparable and reliable data on antibiotic use in Europe from publicly available sources, and to assess the time trends in human exposure to antibiotics. During the pilot phase of this project (November 2001 to October 2003), retrospective data for ambulatory and hospital care was collected for the period 1997 to 2001.

The four objectives of this study were: (i) to describe the characteristics of data sources and data providers per participating country; (ii) to describe the performance of the retrospective data collection process in both ambulatory care and in hospital care; (iii) to describe the approach to methodological problems encountered within the retrospective ESAC project; and (iv) to evaluate the validity of the data obtained for cross-national comparison.

Methods

In this project a 'network of networks' approach was taken. A multidisciplinary management team (a chief microbiologist plus three full-time equivalents in pharmacoepidemiology, medical sociology, pharmacoeconomics and administrative assistance) established a network of dedicated national representatives (predominantly microbiologists), collaborating on a voluntary basis. In each country, the national representative was to contact potential data providers, and to liase with the national body coordinating antibiotic policy (where present) and with the relevant public health authorities. The objective of the central management team was to build viable national data collection networks in each country, in close cooperation with all the interested parties at national level.

All the member states of the EU and all the applicant member states, as well as other countries of the wider European region, were invited to participate.

After a thorough international debate on desirability and feasibility, the following common goals were set: to collect data on the consumption of systemic antibiotics for human use, to collect quarterly data and to collect data for ambulatory and hospital care separately, pertaining to the period 1997 to 2001. Data collection was expected to be aggregated at the level of the active substance (not at brand level), using the taxonomy of the Anatomical Therapeutic Chemical (ATC) classification system, as recommended by the World Health Organization (WHO) [6]. We limited the data collection to the ATC class J01, excluding antifungals, antibacterials for tuberculosis, antitumoral antibiotics, as well as topical antibiotics.

Consumption was to be expressed not in grams or number of boxes sold, but in defined daily doses (DDD) [6]. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is a unit of measurement and does not reflect precisely the recommended or prescribed daily dose. As the ATC/DDD system is a dynamic system which is updated annually, data collected on the basis of previous versions had to be reformatted into the 2002 version [7, 8].

Through a questionnaire to be filled out by the national representatives, additional information was collected on the characteristics of the data sources and data providers (separately for ambulatory and hospital care). We evaluated whether the data covered less than 90% of the national population (sample or incomplete census data) or 90% and more (census data), and, if applicable, the method of data extrapolation or weighting to estimate the consumption of antibiotics in the total population.

Specific details were requested for antibiotic consumption in nursing homes, in dental care and in specialist care to outpatients, in order to establish how the split was made between ambulatory care and hospital care in each country.

Information was gathered regarding the nature of the ATC/DDD assignment process (the authors of the link between consumption data and the ATC/DDD classification; the version used; the handling of missing ATC codes and DDD values, etc.). Finally, we collected information on the mid-year population of the country

for ambulatory care, and on the number of bed days for hospital care, to calculate population-based measures of antibiotic exposure.

Data on antibiotic consumption were collected from either distribution or reimbursement systems. Distribution or sales data were based on reports from the pharmaceutical companies, wholesalers, pharmacies or market research companies. Reimbursement data were collected by the third-party payer on the basis of financial claims from legitimate beneficiaries, from prescribers or from dispensing pharmacies (community or hospital).

Prior to the interpretation of the consumption data, the validity of the consumption data provided was evaluated by means of a checklist including possible sources of bias (Table 1). This checklist was developed during the project, as experience with methodological problems grew. During the project, feedback on problems with the dataset was given to the national representatives, who discussed this with their data providers. Where possible, corrective action was taken. After this round of corrections, the validity of the datasets was evaluated using the checklist with possible biases and scored into three categories: valid data; data considered valid but with minor biases not invalidating the estimate of exposure; invalid data with major biases invalidating the estimate of exposure. Posters with preliminary results and validity scores per country were first discussed at an internal meeting of all the national representatives in Bath, UK, in November 2002, and later presented at the 13th Meeting of the European Society of Clinical Microbiology and Infectious Diseases in Glasgow, Scotland, in May 2003.

Results

Thirty-one countries participated. All 15 countries of the EU, 11 of the 13 applicant countries (not Cyprus and Estonia), and five other countries joined the project (Croatia, Iceland, Norway, Russia and Switzerland). Three countries were not able to deliver data (Romania, Switzerland, and Russia).

Twenty-one countries delivered both ambulatory care and hospital care data separately. Among the remaining seven countries, Iceland could only deliver aggregated total data; Bulgaria only total and hospital care data; Austria, Ireland, Turkey and UK (limited to England only) only ambulatory care data; and Malta only hospital care data.

Characteristics of data providers

Antibiotic consumption data were provided by a wide range of reliable providers, described per country in Table 2. These included health insurers, regulatory authorities, scientific institutions, and professional associations of healthcare providers (pharmacists). Data from Turkey and Croatia were obtained by private market research organizations.

Data collection performance in ambulatory care

Ambulatory care data were available from 25 countries, originating from the distribution chain in 13 countries and the reimbursement systems in 12 countries

Table 1
Checklist for evaluating the validity of the data

1. Problems with population coverage
1.1. Sample bias in samples of less than 90% of the population, not or incorrectly extrapolated.
1.2. Census bias in census data, covering less than 90% not or incorrectly extrapolated.
1.3. Census bias in census data, covering at least 90% but ≤100%: with significant differences in consumption between rest of population and population covered, not properly weighted.
1.4. Underdetection bias in countries where the reimbursement system does not cover substantial segments of the population (in data collection systems based on reimbursement data).
1.5. Underdetection or overdetection bias by parallel import and export (in data collection systems based on distribution data).
2. Problems with drug coverage
2.1. Underdetection bias by over-the-counter (OTC) sales (in data collection systems based on reimbursement data).
2.2. Underdetection bias in countries where specific classes of antibiotics are excluded from reimbursement (in data collection systems based on reimbursement data).
2.3. Measurement bias by problems with Anatomical Therapeutic Chemical Classification (ATC)/defined daily dose (DDD) assignment.
3. Problems with ambulatory care/hospital care mix
3.1. Assignment of data from nursing homes, day care centres and dental care to one of both settings (AC or HC).
3.2. Assignment of specialist prescribing (prescribing by specialists based in ambulatory care; prescribing by hospital-based specialists to outpatients; dispensing by hospital pharmacists to outpatients).

Table 2
Specific providers of data on antibiotic consumption per country

Country	Data sources and providers
Austria	Social Insurance Companies provided reimbursement data (100% coverage).
Belgium	Reimbursement data (90.5% of population covered) are available by law from the community and hospital pharmacies, which transmit to the health insurers and the National Institute for Health Insurance.
Bulgaria	Sales data for 1999 and 2000 were provided by the Bulgarian Drug Agency. Consumption data of one hospital (the main multipurpose hospital in Sofia) were available, covering a period of 5 years.
Croatia	Sales data were collected by a market research company and provided in collaboration with the National Institute of Public Health and the National Institute for Statistics, with almost 100% coverage for ambulatory and hospital care.
Czech Republic	The Institute for Health Information and Statistics (Ministry of Health) delivered reimbursement data provided by the health insurers, covering nearly 100% of the insured population, but without guarantee of comprehensiveness. In hospital care, only one hospital has provided data up to now.
Denmark	Sales data were collected from the community pharmacies and hospital pharmacies, and are provided by the Danish Medicines Agency.
Finland	Complete sales data were provided by the National Agency for Medicines, for ambulatory care as well as hospital care.
France	Sales data were provided by the French Health Products Safety Agency and collected on the basis of mandatory annual reporting by the pharmaceutical companies.
Germany	Ambulatory care data were provided by the WIdO (scientific institute of the AOK health insurance company) using a 0.4% sample for the years before 2000, and a total compulsory health insurance prescription database for the year 2001. Hospital care data were estimated from the SARI project covering 35 intensive care units located in 17 different regions, and from the MABUSE programme covering the medical and surgical services of eight university hospitals.
Greece	Sales data were provided by the National Organization for Medicines and collected on the basis of mandatory reporting by the pharmaceutical companies.
Hungary	Complete reimbursement data for the period 1998–2001 were provided by the National Health Insurance for ambulatory care. For hospital care, complete sales data (only for 2001) were delivered by the same data provider.
Iceland	Total sales data from pharmaceutical companies were provided by the Ministry of Health. No differentiation between ambulatory and hospital care use could be made.
Ireland	Reimbursement data were provided by the GMS (General Medical Services). The data cover 32% of the population and approximately 75% of the overall drug consumption. The GMS Payments Board receives copies of all prescriptions written for GMS patients as part of pharmacists' claims for payments.
Italy	Sales data per year for the period 1999–2001, covering 90% of the population, were provided by the Ministry of Health. Prescribed, nonreimbursed and OTC antibiotics were all included. For hospital care, data were collected from one hospital for the period 1997–2000 and from six hospitals for 2001.
Latvia	The State Medicinal Agency only provided 2001 sales data from wholesalers, separately for ambulatory and hospital care. Validation of the use of the ATC methodology, comprehensiveness of the data, and details on the split between ambulatory and hospital care could not be assessed.
Lithuania	Ambulatory care data—provided by the State Patient Fund—are not comprehensive, because of the complex nature of the reimbursement status of antibiotics (only a limited number of antibiotics are reimbursed, only for special categories of patients and certain diseases). Hospital care data stem from a sample of five hospitals, which cover up to 15% of the total patient days.
Luxemburg	Reimbursement data for ambulatory care were provided by the National Health Insurance Company. Hospital care data were collected by hospital pharmacists.
Malta	No ambulatory care data are available. For hospital care, comprehensive data are collected by the Government Pharmaceutical Services.
The Netherlands	Ambulatory care data were collected and analysed by the Foundation of Pharmaceutical Statistics and provided by the SWAB (Stichting Werkgroep Antibioticabeleid); data from a sample of 88% of community pharmacies were weighted and extrapolated. For hospital care, SWAB requested data from all Dutch hospital pharmacists; 60 hospitals responded (62% bed days) and the results were extrapolated.
Norway	Total sales data were provided by the National Institute of Public Health. For 1998 and 2001, separate hospital care data were available and the differentiation between ambulatory care and hospital care could be made by subtracting hospital care use from the total use.

Table 2
Continued

Country	Data sources and providers
Poland	Sales data were provided by the National Institute for Public Health, for ambulatory care as well as hospital care. Data were derived from 200 out of 400 wholesalers (covering about 60% of the market) and were extrapolated for coverage of the complete population.
Portugal	Reimbursement data for ambulatory care, covering 75% of the population, were provided by the Ministry of Health. For hospital care, only data for 1998 could be delivered.
Slovakia	Wholesaler data were provided by the Slovak Institute for Drug Control. Since 1999 data have been split between ambulatory and hospital care delivered on a monthly basis.
Slovenia	Data were provided by the Institute of Public Health with 100% coverage for ambulatory care. In hospital care, hospital pharmacists provided the data. The coverage of bed days between 1998 and 2001 was 85%, 89%, 98% and 100%, respectively.
Spain	Reimbursement data for ambulatory care were provided by the Spanish Drug Agency and obtained from the ECOM (Especialidades Consumo de Medicamentos) database of the Ministry of Health; hospital care data were provided by the Society of Hospital Pharmacists, and include 15% of hospitals (predominantly large hospitals).
Sweden	Sales/prescription data was provided by the National Corporation of Swedish Pharmacies (Apoteket AB).
Turkey	Only incomplete sales data expressed in units were available from a market research company for ambulatory care. The ATC-DDD methodology was not used: data were expressed in units per 1000 inhabitants per day, which did not allow direct comparison with other countries.
UK/England	Reimbursement data with >95% coverage for ambulatory care were provided by the Department of Health based on the PCA (Prescription Cost Analysis) database, which covers all prescriptions which are dispensed in the community in England. No data were available for hospital care.

(Table 3). Twenty of the 25 countries delivered census data of 90% or more, three delivered incomplete census data (30–78%), and two delivered sample data (25–60%). Seventeen countries were able to provide ambulatory data on a quarterly basis for at least 1 year of the study period.

Data collection performance in hospital care

Hospital care data were available from 23 countries. As hospitals are budgeted in most countries, hospital care data were distribution data in all countries but Belgium. Census data covering at least 90% of the population were provided in 14 countries (Table 3). Sample data were collected in nine countries, ranging from 5 to 62% population coverage. Eight countries were able to provide quarterly data in at least 1 year of the study period.

Approach to methodological problems encountered

Problems with population coverage In a number of countries, data stems from samples that cover <90% of the population. In ambulatory care, three of the 25 datasets were samples that did not allow valid extrapolation (Ireland, Lithuania, Turkey). Valid extrapolation was possible in two countries (Poland, Portugal). In hospital care valid extrapolation was impossible in seven of the 23 datasets (Bulgaria, Czech Republic, Germany, Italy, Lithuania, Portugal and Spain); in two samples (the Netherlands and Poland) a credible extrapolation was made, based on stratification of the participating hospitals.

Even in data collection systems where at least 90% but <100% of the population is covered, census bias may still exist. It may be caused by slight variations in the exact number of insured persons. Some countries extrapolated to the whole population, others did not, based on the assumption that the consumption of non-insured patients was channelled to the insured patients and was paid for by insured patients. There may be substantial differences in the small segment of the non-insured population (the very poor in some countries and the very rich in other countries), but none of the countries had a procedure for weighting for these differences. In the Netherlands, a small part of the population is served by dispensing general practitioners in rural areas.

In many European countries, the reimbursement system is universal and covers (almost) the entire population. Countries where this is not the case have switched to collecting distribution data, to provide a better estimate of population exposure. Two countries, however, were only able to provide reimbursement data for a limited (and underprivileged) segment of

Table 3
Source and coverage (%) of data on antibiotic consumption in ambulatory and hospital care per country

	Ambulatory care		Hospital care	
Country	Type of data*	Coverage of data (%)	Type of data*	Coverage of data (%)
Austria	R	90–100	No data available	
Belgium	R	90	R	95
Bulgaria	Separate AC data not available		D3	<10 (sample data)
Croatia	D4	>95	D4	>95
Czech Republic	R	30–100	D3	<5 (sample data)
Denmark	D3	100	D3	100
Finland	D2	100	D2	100
France	D1	100	D1	100
Germany	R	90	D3	<10 (sample data)
Greece	D1	100	D1	100
Hungary	R	100	D3	100
Iceland	Separate AC data not available		Separate HC data not available	
Ireland	R	35 (incomplete census)	No data available	
Italy	R	90	D3	<5 (sample data)
Latvia	D2	90	D2	90
Lithuania	R	20–40 (incompl.census)	D3	<15 (sample data)
Luxemburg	R	96	D3	90
Malta	No data available		D3	97
the Netherlands	D3	90	D3	62 (sample data)
Norway	D2	100	D3	100
Poland	D2	60 (sample data)	D2	60 (sample data)
Portugal	R	78 (incomplete census)	D3	<50 (sample data)
Slovakia	D2	100	D2	100
Slovenia	D2	100	D3	85–100
Spain	R	100	D3	15 (sample data)
Sweden	D3	100	D3	100
Turkey	D4	<25 (sample data)	No data available	
UK/England	R	100	No data available	

**D, Distribution; R, reimbursement; 1, manufacturers; 2, wholesalers; 3, pharmacies; 4, marketing research companies.*

their population, namely Lithuania (40%) and Ireland (35%).

In countries with data collection based on distribution data and with substantial parallel export, the validity of the population exposure estimate may be distorted (e.g. Greece up to 10% overestimation of consumption).

Problems with drug coverage In countries with data collection systems based on reimbursement data and with substantial over-the-counter (OTC) sales, significant underdetection bias is possible. This was documented in Spain (about 10% underestimation of consumption) and suspected in Italy and Portugal.

Datasets based on distribution data are less vulnerable to this source of bias, as they cover the sales of all prescribed OTC antibiotics, whether or not they are reimbursed.

In many European countries, all antibiotics are at least partially reimbursed and therefore data collection based on reimbursement data will not be biased. However, in some countries several antibiotics are excluded from the reimbursement list, either because they are too expensive, too inexpensive or considered inappropriate (Denmark) or because their reimbursement is limited to certain diagnoses or population groups (Lithuania). In some countries, part of initial antibiotic usage is not reimbursed when it forms part of a deductible sum that has to be paid in full by the patient (Denmark, Iceland, Ireland, Sweden). These particularities of the reimbursement system do not hamper data collection when the countries concerned collect distribution data (Denmark, Iceland, Sweden). Additionally, reimbursement in some countries might not include antibiotics when they are cheaper than a fixed fee for prescription (Austria, Ger-

many, UK), but the potential effect on data collection in these countries was considered minute. Only in Lithuania and Ireland was the validity of data collection seriously hampered by the limitations of the reimbursement system, as in those two countries no alternatives to reimbursement data were publicly available.

Compliance with the ATC/DDD classification has been a major issue in the ESAC pilot project. All countries (except Turkey) were able to aggregate their consumption data in terms of the ATC Classification. All countries stated that they had used the ATC/DDD 2002 version for the retrospective period of 1997–2001, but several adjustments were necessary (e.g. in some countries data on urinary antiseptics were not recalculated after the switch in 1999 from G04 to J01MB, J01XE and J01X and consumption for these products was initially not recorded before 2000). Local *ad hoc* assignments of DDDs, deviating from the official DDD (e.g. higher *ad hoc* DDDs for amoxiclav in several countries), were observed and corrected. New antibiotics on the market, such as telithromycin and linezolid, had not yet been assigned in the 2002 version of the ATC classification and their initial use was often not properly reported. For 23 older antibiotics (e.g. benzathine benzylpenicillin and benzathine phenoxymethylpenicillin) and 19 antibiotic combinations (e.g. sulfametrole plus trimethoprim), no official DDD was initially assigned by the WHO Collaborating Centre in Oslo. Their consumption remained either undetected or was misclassified. For example, in Croatia, no DDD was assigned to benzathine phenoxymethylpenicillin, a narrow-spectrum penicillin used extensively in this country. Because of the absence of DDD assignment, the consumption of this substance was not recorded, leading to a substantial underestimation of consumption in this class.

Problems with ambulatory care/hospital care mix The last source of potential bias concerns the proper determination of the mix between ambulatory and hospital care. In Iceland and Bulgaria, it was not possible to split the total data originating from wholesalers. In other countries, substantial variation was observed between the methods used to separate ambulatory and hospital care data. Most problematic here was the status of nursing homes. Antibiotic consumption in these institutions might be substantial in a number of countries [9, 10]. In 14 countries, consumption data from nursing homes were allocated completely to ambulatory care, in five countries they were partly allocated to ambulatory care, in two countries they were completely allocated to hospital care and in four countries the allocation of antibiotic use data was unknown. Similarly, caution is to be exercised with the attribution of consumption in day care centres and with prescriptions written by dentists. Attribution of specialist prescribing is another tricky issue. In some countries, the healthcare system allows for private specialists working in primary care outside the hospital, and their prescriptions are attributed to primary care, while in other countries this kind of service does not exist. In some countries, prescriptions by hospital-based specialists to outpatients (polyclinic prescribing) are dispensed in the community pharmacy, in other countries in the hospital pharmacy. In some countries, the hospital consumption of a limited number of small private hospitals may be attributed to ambulatory care (the Netherlands, Greece). Finally, hospital pharmacies in some countries are allowed to dispense a limited number of pharmaceuticals (e.g. AIDS or antitumour medication) to outpatients (e.g. Belgium). In most countries, these problems with determining the mix between ambulatory and hospital care probably caused only minor biases. In Finland and Latvia, however, the split between ambulatory care and hospital care was considerably distorted.

A final methodological aspect was the denominator problem. It was easy to find data on the mid-year population of each of the countries from traditional databases providing statistical data. It proved to be more difficult to find reliable data on hospital bed days. Definitions and calculation methods for bed days differ from country to country. Data on bed days at the national level are difficult to access in many countries, since they are often only available on a yearly basis and with considerable delay. In international databases (at the WHO or the Organization for Economic Co-operation and Development) inexplicable discrepancies were found among data on bed days. Moreover, in many countries no reliable and timely data on the apportionment of acute, chronic and psychiatric beds are available. For the ESAC project, trying to express national hospital consumption in terms of DDD per 100 bed days was considered impractical, unreliable and not useful. For this reason, hospital care consumption data were expressed in DDD per 1000 inhabitants per day, as there seems to be a strong correlation between the mid-year population and the number of bed days in European countries [11].

Evaluation of the validity of the dataset

Detailed information per year and per country regarding the availability and the validity of antibiotic consumption data in Europe for the period 1997–2001 is given in Table 4. For ambulatory care, the estimate of exposure was valid (or only slightly biased) for international

Table 4
Availability of data on volume of utilization of antibiotics (ATC J01) in Europe within the ESAC project (1997–2001)

	1997			1998			1999			2000			2001		
	AC	HC	TC	AC	HC	TC	AC	HC	TC	AC	HC	TC	AC	HC	TC
European Union Countries															
Austria	–	–	–	⊙	–	–	⊙	–	–	⊙	–	–	⊙	–	–
Belgium	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Denmark	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Finland	●	⊙	●	●	⊙	●	●	⊙	●	●	⊙	●	●	⊙	●
France	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Germany	●	–	–	●	○	○	●	○	○	●	○	○	●	–	–
Greece	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙
Ireland	Participant who provided data but not in time														
Italy	–	○	–	–	○	–	●	○	○	●	–	–	●	–	–
Luxemburg	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
The Netherlands	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	–	–
Portugal	●	–	–	●	○	○	●	–	–	●	–	–	●	–	–
Spain	⊙	○	○	⊙	○	○	⊙	○	○	⊙	○	○	⊙	○	○
Sweden	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
UK/England	●	–	–	●	–	–	●	–	–	●	–	–	●	–	–
Applicant countries (first and second wave)															
Bulgaria	–	○	–	–	○	–	–	○	⊙	–	○	⊙	–	○	–
Cyprus	Country not yet participating in ESAC														
Czech Republic	–	–	⊙	●	–	⊙	●	–	⊙	●	–	⊙	●	○	⊙
Estonia	Country joining ESAC at a later stage														
Hungary	–	–	–	●	–	–	●	–	–	●	–	–	●	●	●
Latvia	–	–	–	–	–	–	–	–	–	–	–	–	○	○	⊙
Lithuania	–	–	–	–	–	–	–	–	–	○	–	–	○	○	○
Malta	–	●	–	–	●	–	–	●	–	–	●	–	–	●	–
Poland	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙
Romania	Participant not yet able to provide data														
Slovakia	–	–	●	–	–	●	●	●	●	●	●	●	●	●	●
Slovenia	●	○	○	●	●	●	●	●	●	●	●	●	●	●	●
Other European countries															
Croatia	–	–	–	–	–	–	–	–	–	●	●	●	●	●	●
Iceland	–	–	●	–	–	●	–	–	●	–	–	●	–	–	●
Norway	–	–	●	⊙	⊙	●	–	–	●	–	–	●	⊙	⊙	●
Russia	Participant not yet able to provide data														
Switzerland	Participant not yet able to provide data														
Turkey	○	–	–	○	–	–	○	–	–	○	–	–	○	–	–

AC, Ambulatory care; HC, hospital care; TC, total care; –, no data provided; ○, data with major bias, invalidating exposure estimation; ⊙, data available in defined daily doses (DDD), but with minor bias, not invalidating exposure estimation; ●, valid data available in DDD.

comparison in 21 countries (14 for all 5 years). Of these, 17 countries provided data on a quarterly basis for at least 1 year (10 for all 5 years).

For hospital care, 14 countries were able to deliver valid data (nine for all 5 years).

A valid estimate of the total exposure of national populations to human antibiotic consumption could be made in 17 countries.

Discussion

The ESAC pilot project formed a step forward in the ability to gather reliable drug utilization data from public sources for cross-national comparison. This achievement was made possible by voluntary cooperation of national representatives of a dynamic scientific society, the logistic support of a multidisciplinary central management team, and adequate funding from the European

Health authorities. The ESAC project was instrumental in the now almost universal adoption of the ATC/DDD methodology in Europe. By investing in national network development, a foundation was laid for sustainable efforts in valid data collection, although this foundation is still precarious in the countries of Eastern Europe. Factors which facilitated the project were the establishment of general Drug Utilization Monitoring systems in many European countries and the existence of national coordination committees for antibiotic policy, created in response to the 1998 Copenhagen Declaration of the 'Microbial threat'.

Several blank areas remain on the European map on completion of the pilot project, but prospects are favourable for charting this 'terra incognita' in the next few years by means of a sustained data collection effort.

It is clear from this project and previous attempts [12–14] that methodological rigour is needed to assure the validity of the data and to ensure reliable cross-national comparison. Corrections need to be made for bias by parallel export and OTC sales. Bias by incomplete census must be documented and corrected. As there is no European administrative drug database, the attribution of national brands to specific ATC classes and the local calculation of the number of defined daily doses in medicinal product packages needs to be validated in national registers. In future data collection efforts, each country should send in a register of all medicinal product packages assigned to the ATC class J01 (systemic antibiotics for human use), including the exact specification of attribution to the ATC5 code and the calculation of the number of DDDs per package for each marketed medicinal product package. In addition, sufficient information on active ingredients, strength and pack size should be provided to enable a thorough check of this calculation.

Much is still to be gained from extending the scope, depth and validity of the data. Especially in hospital care, samples need to be extended to cover all hospitals, if possible with a breakdown by individual hospital, to account for variable consumption among institutions within the same country. Countries which rely on data collection systems based on sales data from pharmaceutical companies and wholesalers should consider making significant changes, because the future lies in collecting data with more clinical content, allowing the use of more sophisticated health indicators. Improvements can be made to the speed of data collection, to create an early warning system for questionable consumption patterns.

The approach to data collection and validation in the field of antibiotics may be useful to develop drug utilization monitoring systems in other pharmacological fields or even to survey the entire spectrum of medication utilization. However, this will require considerable effort.

Meanwhile, sustaining the results of the ESAC project may prove difficult. The Eastern European countries in particular will need logistic support to make the transition from a data collection system based on a central wholesaler to new, but equally reliable systems. The complex organization of the EU, extended to include new member states, makes the creation and maintenance of a coordinated consumption surveillance system a daunting task. On the other hand, the heterogeneity of antibiotic use in European countries may offer better insights into the dynamics of antibiotic resistance on a large, international scale.

A procedure has been established to assure access for scientists and regulators to the data on the ESAC website by submitting protocol-based requests. Hopefully, it will be possible to continue the ESAC data collection and the ensuing service to the healthcare community.

Challenging analyses of the correlation between consumption, determinants of use [15, 16] and resistance [17] can be further explored. By providing a core set of data valid for cross-national comparison, at least one of the pitfalls of ecological research has been eliminated. Moreover, the availability of quarterly consumption data over a period of 5 years enables comparisons with time series of epidemiological data on the incidence of infectious diseases and the emergence of resistance over prolonged periods. Rates of resistance remain low in Northern European countries, but climb in Southern and Central European countries [18]. In some instances of resistance, the major selective pressure driving changes in the frequency of resistance is the volume of antimicrobial use. Indeed, several studies have shown that the variation in resistance of *Streptococcus pneumoniae* to β-lactams and macrolides was best explained by geographical variation in selection pressure for resistance [17, 19]. Thus, surveillance programmes on antibiotic resistance should be accompanied by programmes to monitor antibiotic consumption, using common drug classification systems, and gathering reliable drug utilization data to perform valid cross-national ecological studies on antibiotic resistance and usage.

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